



מדינת ישראל
STATE OF ISRAEL

REC'D 14 JUL 2004
WIPO PCT

Ministry of Justice
Patent Office

משרד המשפטים
לשכת הפטנטים

BEST AVAILABLE COPY

This is to certify that
annexed hereto is a true
copy of the documents as
originally deposited with
the patent application
particulars of which are
specified on the first page
of the annex.

זאת לתעודה כי
רצופים בזה העתקים
נכונים של המסמכים
שהופקדו לכתחילה
עם הבקשה לפטנט
לפי הפרטים הרשומים
בעמוד הראשון של
הנספח.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)



22-05-2004
This היום
רשם הפטנטים
Commissioner of Patents

נתאשר
Certified

מספר:

Number

156626

תאריך:

Date

24-06-2003

הוקדם/נדחה

Ante/Post-dated

בקשה לפטנט

Application for Patent

אני, (שם המבקש, מענו - ולגבי גוף מאוגד - מקום התאגדותו)

I (Name and address of applicant, and, in case of a body corporate, place of incorporation)

Yeda Research and Development Co. Ltd.

at the Weizmann Institute of Science

P.O. Box 95

76100 Rehovot

ידע חברה למחקר ופיתוח בע"מ

ליד מכון ויצמן

ת.ד. 95

רחובות 76100

Inventor/s: Yaron SILBERBERG; Dvir YELIN; Dan ORON

הממציא/ים: ירון זילברברג; דביר ילין; דן אורון

ששמה הוא:

בעל אמצאה מכח העברה

Owner, by virtue of an assignment

of an invention, the title of which is:

שיטה ומערכת להריסת תאים סלקטיבית

(בעברית)

(Hebrew)

METHOD OF AND SYSTEM FOR SELECTIVE CELL DESTRUCTION

(באנגלית)

(English)

hereby apply for a patent to be granted to me in respect thereof.

מבקש בזאת כי ינתן לי עליה פטנט.

*בקשת חלוקה Application for Division		*דרישת דין קדימה Priority Claim		
*מבקשת פטנט from Application		מספר/סימן Number/Mark		מדינת האיגוד Convention Country
No. _____ dated _____				
*מס' _____ dated _____				
*מס' _____ dated _____				
*יפוי כח: כללי / מיוחד - צריך להיות / עוד יוגש P.O.A.: general / specific - attached / to be filed later Has been filed in case _____ הוגש בענין _____				
Address for Service in Israel המען למסירת הודעות ומסמכים בישראל				
G.E. Ehrlich (1995) Ltd. 28 Bezalel Street 52 521 Ramat Gan		ג'י. אי. ארליך (1995) בע"מ רחוב בצלאל 28 רמת גן 52 521		
חתימת המבקש Signature of Applicant		היום 23 בחודש יוני שנת 2003		
		This 23 of June 2003		
For the Applicant				
Attorney Docket No.: 26186				

לשימוש הלשכה
For Office Use

שיטה ומערכת להריסת תאים סלקטיבית

METHOD OF AND SYSTEM FOR SELECTIVE CELL DESTRUCTION

METHOD OF AND SYSTEM FOR SELECTIVE CELL DESTRUCTION

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a method and system for destruction
5 of biological tissues and/or cells via selective ionization and, more particularly, to a method of ionizing biological tissues and/or cells using metallic nano-particles and electromagnetic irradiation.

Cancer is a major cause of death in the modern world. Effective
treatment of cancer is most readily accomplished following early detection
10 of malignant tumors. Most techniques used to treat cancer (other than chemotherapy) are directed against a defined tumor site in an organ, such as brain, breast, ovary and colon tumors, etc. When a mass of abnormal cells is consolidated and is sufficiently large, either surgical removal,
destruction of the tumor mass using either heating, cooling, radiative or
15 chemical ablation becomes possible because the target is readily identifiable and localizable. However, it is not uncommon for a cancer that has initially occurred at a primary site to metastasize and spread into adjacent organs as diffuse clusters of abnormal cells. These small clusters
of cells, which are more properly referred to as microscopic diffuse
20 metastatic deposits, are not localizable and are virtually impossible to treat other than by systemic chemotherapy or radiotherapy. Yet, because of the diverse nature of cancer cells, only a portion of the metastatic abnormal cells will likely be susceptible to chemotherapy or radiotherapy, leaving
abnormal cells that are resistant to the therapy to multiply until the patient
25 dies from the concomitant effects of the malignant cells.

Recently, light and more specifically laser light has been used for
non-invasive detection as well as destruction of malignant cells. Laser
technology has found many applications in medicine and biology including
destruction of cells or tissues, e.g., for the purpose of cancer treatment.
30 Destruction of unwanted cells can be achieved either through a direct

interaction between the laser beam and the tissue, or through activation of some photochemical reactions using light-activated molecules which are injected into or otherwise administered to the tissue.

Photo-dynamic therapy (PDT) is a relatively new approach for treating many cancers. At the first step of treatment, one or more drugs that bind to rapidly dividing cells are administered either directly to a tissue or organ or systemically to the treated subject. The drugs administered for PDT are commonly known as photosensitizers due to their inherent ability to absorb photons of light and transfer that energy to oxygen which then converts to a cytotoxic or cytostatic species. Approximately 24-48 hours after the injection, a narrow-band laser is used to excite the photosensitive drug, inducing a chemical reaction which results in a production of free radicals and/or other reactive products that destroy the abnormal tissue or cell with relatively small damage to the surrounding healthy tissue.

To date, PDT has been used to treat esophageal cancer, early stage lung cancer, Kaposi's sarcoma, an AIDS related condition, atherosclerotic plaques, lesions of surface skin diseases, overgrowth of blood vessels in the eye (macular degeneration) and unwanted pathogens in the blood.

The effectiveness of the PDT process depends on the amount of photosensitizer at the target, the absorption properties of the environment neighboring the target and photosensitizer, and a number of physiologic factors such as temperature, pH, oxygen content, and the sensitivity of the target to the photosensitizer generated reaction.

Known PDT techniques suffer from a number of drawbacks and limitations. It is necessary to deliver a large amount of light radiation to the tumor at specific wavelengths to activate the photosensitive agent. Most photosensitive agents are activated at wavelengths that can only penetrate through three or less centimeters of tissue. Hence, non- or minimal-invasive PDT can be used for cancerous growths that are on or near the surface of the skin, or on the lining of internal organs.

Typical prior art PDT light delivery systems have used monochromatic lasers in combination with fiber optic catheters, for example by providing a monochromatic light to a fiber optic bundle, which in turn transmits the light through a light diffuser to the tumor. One
5 disadvantage of such PDT delivery system is that a typical fiber optic catheter transmits only about 30 % to 50 % of available light energy. Additional energy losses occur in the diffuser which surrounds the light-emitting end of the catheter and diffuses the light emanating from the catheter. The blood and the surrounding tissue also attenuate a substantial
10 portion of the input power. The net result is that only about 25 % to 30 % of the power is available to activate the photosensitive agent. Besides increasing the required size and cost of the light source, these energy losses also reduce the effectiveness of the treatment since the depth of radiation penetration into the tissue is reduced. With reduced penetration, surgical
15 techniques are required to remove much of the malignant tissue before photodynamic therapy commences, and the likelihood that all malignant tissue is destroyed is lessened.

Another drawback of PDT techniques is that the photosensitizing drug remains in the bloodstream for six weeks or more, causing patients to
20 be extremely light sensitive during that time period.

The present invention provides solutions to the problems associated with prior art cell destruction techniques.

SUMMARY OF THE INVENTION

25 According to one aspect of the present invention there is provided a method of destroying living cells, the cells being characterized by an ionization threshold, the method comprising: providing at least one optical pulse having an optical field power smaller than the ionization threshold of the cells; and generating conditions for locally increasing the optical field

power per unit area beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

According to further features in preferred embodiments of the invention described below, the generating conditions for locally increasing the optical field power per unit area is by a plurality of particles, at least a portion of each of the plurality of particles is made of a conducting material.

According to another aspect of the present invention there is provided a method of destroying living cells, the cells being characterized by an ionization threshold, the method comprising: administering a plurality of particles to the cells, at least a portion of each of the plurality of particles is made of a conducting material; and directing at least one optical pulse toward at least a portion of the cells; the particles and the at least one optical pulse are selected and designed so as to provide a local enhancement of an optical field to a power per unit area which is beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

According to further features in preferred embodiments of the invention described below, the method further comprising focusing a beam of the at least one optical pulse, so as to increase the optical field power per unit area.

According to still further features in the described preferred embodiments the focusing is done by a converging lens.

According to yet another aspect of the present invention there is provided a system for destroying living cells, the cells being characterized by an ionization threshold, the system comprising: an optical device for providing at least one optical pulse having an optical field power which is smaller than the ionization threshold of the cells; and a mechanism for locally increasing the optical field power per unit area beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

According to further features in preferred embodiments of the invention described below, the mechanism for locally increasing the optical field power per unit area comprises a plurality of particles, at least a portion of each of the plurality of particles is made of a conducting material.

According to still further features in the described preferred embodiments the system further comprising at least one optical element for focusing a beam of the at least one optical pulse, so as to increase the optical field power per unit area.

According to still another aspect of the present invention there is provided an ablative procedure for destroying living cells present in a body of a subject, the cells being characterized by an ionization threshold, the ablative procedure comprising: administering a plurality of particles to the body of the subject, at least a portion of each of the plurality of particles is made of a conducting material; directing at least one optical pulse toward at least a portion of the cells; the particles and the optical pulses are selected and designed so as to provide a local enhancement of an optical field to a power per unit area which is beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

According to further features in preferred embodiments of the invention described below, the directing at least one optical pulse is by inserting a light transmitting device into the body of the subject; and using the light transmitting device for

According to still further features in the described preferred embodiments inserting the light transmitting device into the body is by endoscopy.

According to still further features in the described preferred embodiments inserting the light transmitting device into the body is by laparoscopy.

According to an additional aspect of the present invention there is provided a light transmitting device for destroying living cells present in a body of a subject, the device comprising: an optical device for emitting a at least one optical pulse having a duration in a femtosecond time scale; and a
5 waveguide for guiding the optical pulses into a body of a subject; the waveguide having an emission face, through which the optical pulses are emitted to the living cells, thereby destroying the cells via ionization.

According to further features in preferred embodiments of the invention described below, the waveguide comprise a fiber optic bundle.

10 According to still further features in the described preferred embodiments the waveguide is sterile.

According to still further features in the described preferred embodiments the waveguide is covered by a disposable sterile coat.

15 According to still further features in the described preferred embodiments the cells form a part of an organ.

According to still further features in the described preferred embodiments the cells form a part of a tumor.

According to still further features in the described preferred embodiments the cells form a part of a malignant tumor.

20 According to still further features in the described preferred embodiments the cells form a part of a blood vessel.

According to still further features in the described preferred embodiments the cells form a part of a pathological tissue.

25 According to still further features in the described preferred embodiments the cells form a part of a restenotic tissue.

According to still further features in the described preferred embodiments the ionization threshold is from about 10^{10} Watts/cm² to about 10^{14} Watts/cm².

30 According to still further features in the described preferred embodiments the light transmitting device comprises a fiber optic bundle.

According to still further features in the described preferred embodiments a duration of the at least one optical pulse is selected so as to avoid heating of the cells by linear absorption.

5 According to still further features in the described preferred embodiments the duration is in a femtoseconds time scale.

According to still further features in the described preferred embodiments a wavelength of the at least one optical pulse is from about 400 nm to about 1300 nm.

10 According to still further features in the described preferred embodiments a repetition-rate of the at least one optical pulses is from a 10 pulses/second to about 10^{10} pulses/second.

According to still further features in the described preferred embodiments the pulses having a high peak-power.

15 According to still further features in the described preferred embodiments the pulses having a low average-intensity.

According to still further features in the described preferred embodiments the peak-power is below the ionization threshold of the living cells.

20 According to still further features in the described preferred embodiments the average-intensity is below a heating damage threshold of the living cells.

According to still further features in the described preferred embodiments the average-intensity is lower than 1 Watt/cm².

25 According to still further features in the described preferred embodiments the light transmitting device comprises at least one optical element for focusing a beam of said at least one optical pulse, so as to increase said optical field power per unit area.

According to still further features in the described preferred embodiments the at least one optical element is a converging lens.

According to still further features in the described preferred embodiments each of the plurality of particles comprises an affinity component having affinity to the living cells.

5 According to still further features in the described preferred embodiments a size of each of the plurality of particles is from 1 nm to 200 nm.

According to still further features in the described preferred embodiments the particles are biocompatible.

10 According to still further features in the described preferred embodiments the particles are metallic particles.

According to still further features in the described preferred embodiments the conducting material is comprised of at least one metal selected from the group consisting of coinage metals, noble metals, transition metals and synthetic metals.

15 According to still further features in the described preferred embodiments the synthetic metals are selected from the group consisting of polyacetylene and polyaniline.

According to still further features in the described preferred embodiments the conducting material is gold.

20 According to still further features in the described preferred embodiments the conducting material comprises a metal-like material.

According to still further features in the described preferred embodiments the conducting material comprises a metal alloy.

25 According to still further features in the described preferred embodiments the affinity component comprises a moiety selected from the group consisting of an antibody, an antigen, a ligand and a substrate.

According to still further features in the described preferred embodiments the moiety is selected so as to ensure attachment of the particles to a predetermined part of the cell, which is selected from the

group consisting of nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins, endoplasmic reticulum and Golgi apparatus.

According to still further features in the described preferred embodiments the particles comprise a conducting shell layer characterized by a shell-thickness, having a first radius and a second radius.

According to still further features in the described preferred embodiments a ratio between the first radius and the second radius is selected so as to obtain a predetermined plasmon-resonance frequency of the particles.

According to still further features in the described preferred embodiments the predetermined resonance frequency is a near infrared resonance frequency.

According to still further features in the described preferred embodiments the thickness is from 1 nm to 100 nm.

According to still further features in the described preferred embodiments the conducting shell layer immediately adjacent to and independently layered upon a non-conducting core layer.

According to still further features in the described preferred embodiments the non-conducting core layer comprises a dielectric material.

According to still further features in the described preferred embodiments the dielectric material is selected from the group consisting of silicon dioxide, titanium dioxide, PMMA, polystyrene, and dendrimers.

According to still further features in the described preferred embodiments the non-conducting core layer comprises a semi-conducting material.

According to still further features in the described preferred embodiments the non-conducting core layer comprises at least one molecule selected from the group consisting of an organic molecule and an organic super-molecular structure.

According to still further features in the described preferred embodiments the non-conducting core layer comprises a mixture of non-conducting materials.

According to still further features in the described preferred
5 embodiments the non-conducting core layer comprises an optically absorbing material.

According to still further features in the described preferred embodiments the non-conducting core layer comprises a fluorescent material.

10 According to still further features in the described preferred embodiments the optical device has a peak-power from about 10^5 Watts to about 10^{10} Watts.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a method and system for
15 destroying living cells far exceeding prior art.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to
20 the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In
25 this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIG. 1 is a system for destroying living cells, according to the present invention; and

FIG. 2 is a nanoparticle captured in a cell, according to the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a method and a system for destroying living cells by ionization, which can be used for tissue/cell ablation. Specifically, the present invention can be used to remove clusters of cells either by invasive or non-invasive medical procedures.

The principles and operation of a method and a system for destroying living cells according to the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure 1 illustrates a system 10 for destruction of living cells 12. According to the present invention, cells 12 are characterized by an ionization threshold, measurable in units of energy per time unit per area unit, *e.g.*, Watts/cm². Cells 12 may form any part of the human body, for example, an organ or a part of an organ, *e.g.*, a blood vessel or part thereof, a tumor (malignant or benign) and any other pathological tissue, *e.g.*, a restenotic tissue. A typical ionization threshold

for cells 12 is, in terms of orders of magnitude, from 10^{10} Watts/cm² to 10^{14} Watts/cm².

According to a preferred embodiment of the present invention system 10 includes an optical device 14 for providing an optical field power smaller than the ionization threshold and a mechanism 16 for locally increasing the optical field power per unit area beyond the ionization threshold of the cells. The optical field, as provided by optical device 14 is in a form of at least one light pulse (*e.g.*, a sequence of laser pulses), the duration and the repetition-rate of which are chosen so as to avoid heating of the cells by linear absorption. A typical pulse duration is in a femtoseconds time scale, *e.g.*, about $10\text{-}1000\cdot 10^{-15}$ seconds.

As used herein, the term about refers to $\pm 10\%$.

Optical device 14 provides a laser beam having a high peak-power with a low average-intensity. According to a preferred embodiment of the present invention, the peak-power of the laser is below the ionization threshold and the average-intensity is below the heating damage threshold for bodily tissues.

The desired peak and average intensities may be achieved in more than one way. Hence, in one embodiment of the present invention, device 14 may be provided as an amplified, low repetition-rate femtosecond laser system having a peak-power of about 10^{10} Watts. In another embodiment of the present invention, device 14 may be a high repetition-rate femtosecond laser system having a peak power of about 10^5 Watts. It is to be understood that in the latter embodiment the illuminated area should be sufficiently small and the beam should be focused by at least one optical element 18 to achieve high optical field power per unit area at the cell. Optical element 18 may be any known element for focusing (*e.g.* collimating) an optical beam, such as, but not limited to a converging lens.

Typical repetition rates are from about 10 pulses/second for a low repetition-rate laser system to about 10^{10} pulses/second for a high repetition-rate femtosecond laser system. One ordinarily skilled in the art would appreciate that a penetration depth of the laser beam into the body depends on the wavelength of the optical field. It is known that human tissues are relatively transparent to light in the near-infrared region (NIR) of the spectrum. When deep penetration is desired, a preferred wavelength of the laser beam is from about 800 nm to about 1300 nm, however, shorter wavelengths (*e.g.* 400 nm to 800 nm) may also be used, for abnormal cells growths that are on or near the surface of the skin, or on the lining of internal organs.

Unlike prior art teachings, where the power of the laser beam is above the ionization threshold, optical device 14 provides a pulse power which is below ionization threshold hence there is no global cell destruction across the entire illumination area, along its efficient penetration depth.

Mechanism 16 serves, according to the gist of the present invention, for increasing the laser field beyond the ionization threshold only within a limited volume where unwanted cells are present. Thus, system 10 has the advantage of selectively destroying unwanted cells by ionization, while leaving other neighboring cells substantially undamaged.

According to a preferred embodiment of the present invention mechanism 16 may be any mechanism capable of locally increasing the optical field. Thus, for example, mechanism 16 may include a plurality of particles, at least a portion of each of the particles is made of a conducting material. Hence, the particles may be, for example, metallic particles.

Each of the particles may also include an affinity component, whereby the affinity component has affinity to the living cells to be destroyed. The particles have a diameter which is preferably from 1 nm to

200 nm, so as to allow a substantial increment of the nearby optical field, which increment is larger for smaller particles. The affinity component of the particles ensures a short distance between the particles and the unwanted cells, hence when the optical field is increased near the particles, a selective destruction of the cells occurs. When ionization occurs at a living cell, it is destroyed irrespectively to the location at which the ionization is initiated. Thus, the affinity of the particles may be selected so that the particles will attach to any part of the cell, *e.g.*, nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins and the like.

As used herein, the term nanoparticle refers to a particle or particles of nano-meter size range, *e.g.*, $1\text{-}200\cdot 10^{-9}$ m.

The physical process of strong field enhancement very close to metal nanoparticles is a well known phenomenon and has been described in detail in the literature. To this end, see, for example, R. H. Doremus and P. Rao, *J. Mater. Res.*, 11, 2834 (1996); M. Quinten, *Appl. Phys. B* 73, 245 (2001) and R. D. Averitt, S. L. Westcott and N. J. Halas, *J. Opt. Soc. Am. B* 16, 1824 (1999), the contents of which are hereby incorporated by reference.

In metal nanoparticles, resonant collective oscillations of conduction electrons, also known as particle plasmons, are excited by an optical field. The resonance frequency of a particle plasmon is determined mainly by the dielectric function of the metal, the surrounding medium and by the shape of the particle. Resonance leads to a narrow spectrally selective absorption and an enhancement of the local field confined on and close to the surface of the metal particle. The spectral width of absorption and near-field enhancement depends on the decay time of the particle plasmons.

When the laser wavelength is tuned to the plasmon resonance frequency of the particle, the local electric field in proximity to the nano-particles could be enhanced by several orders of magnitude.

Reference is now made to Figure 2, which illustrates a nanoparticle 22 which is captured by one of living cells 12. Nanoparticle 22 includes affinity component 26, which specifically attaches nanoparticle 22 to cell 12. Cell 12 and nanoparticle 22 are illuminated by laser beam 28. The optical field of beam 28 is increased in a volume 24 neighboring nanoparticle 22.

When the optical field interacts with atoms or molecules present in volume 24, the electrons are oscillating due to the force exerts by the field oscillations. When the field power per unit area reaches above the ionization threshold, the electrons detach from the atoms. The free electrons that are formed after the initial ionization are accelerated by the optical field and interact with other molecules, leading to the creation of local damage. Because the pulse power of laser beam 28 is below the ionization threshold of cells 12, the damage is constrained only to volume 24.

The structure size and shape of the nanoparticles are designed in accordance with the specific application for which system 10 is used. Specifically, the size of the nanoparticles is selected so that the resonance frequency of the nanoparticles and the frequency of the optical pulses substantially coincide. Hence, in preferred embodiments in which the pulses are of short wavelengths (*e.g.*, 400-800 nm for near-skin treatments), the nanoparticles are about 1-50 nm in diameter. Longer wavelengths (*e.g.*, near infrared), which allow deep penetration depth of the optical pulses into the body, require larger nanoparticles, about 100-200 nm in diameter.

It is often desired to further minimize the nanoparticles size, for example, to enhance the effect of optical field increment or to allow the nanoparticles to penetrate into the cells. This may be done, by providing nanoparticles which include a dielectric core and a conducting shell layer.

Nanoparticles having such structure are called nanoshells. Although nanoshells are especially useful in cases of near infrared wavelengths applications, they may also be used for short wavelengths applications.

The process of manufacturing nanoshells having a dielectric core and a conducting shell, is known in the art and is described in, for example, WO 01/06257 and WO 02/28552, the contents of which are hereby incorporated by reference.

For any given core and shell materials, the ratio between the core radius and the total radius of nanoshells can be chosen for maximum scattering and minimum absorption at a specific resonance frequency. Based on the core to total radii ratios, the nanoshells manifesting plasmon resonances extending from ultraviolet to infrared can be readily fabricated. Hence, the core diameters of the nanoshells may range from about 1 nm to about 400 nm or more, and the shell thickness may range from about 1 nm to about 100 nm. For a near infrared light, the total diameter of the nanoshells may be reduced down to 20 nm.

According to a preferred embodiment of the present invention the non-conducting core layer may be, for example, a semi-conducting material, an organic molecule, an organic super-molecular structure, or any mixture of non-conducting materials. Optionally, the non-conducting core layer may include an optically absorbing material, and/or a fluorescent material.

According to another aspect of the invention there is provided a method of destroying living cells, characterized by an ionization threshold.

The method comprises the following steps which may be executed using an appropriate system, device or apparatus, *e.g.*, system 10, as described hereinabove. Hence, at least one optical light pulse is provided, having an optical field power smaller than the ionization threshold of the cells, while generating conditions for locally increasing the optical field power per unit area beyond the ionization threshold of the cells. Hence the cells are

destroyed via ionization. The conditions for locally increasing the optical field may be generated, for example, by administering particles such as, *e.g.*, nanoparticles 22 to the cells, as is further detailed hereinabove.

According to an additional aspect of the invention there is provided
5 a light transmitting device for destroying living cells present in a body of a subject. The device may be used, *e.g.*, by system 10, as optical device 14 (Figure 1). According to a preferred embodiment of the present invention the device includes an optical device for emitting at least one optical pulse having a duration which is preferably in a femtosecond time scale. The
10 device further includes a waveguide, *e.g.*, fiber optic bundle, for guiding the optical pulses into a body of a subject. The waveguide having an emission face, through which the optical pulses are emitted to the living cells, hence the cells are destroyed as detailed above. The device may be used either in an invasive medical procedure or in non-invasive medical
15 procedure. In any case, the waveguide is preferably sterile. The sterilization of the waveguide may be, for example by a disposable sterile coat, which covers at least a portion of the waveguide.

The present invention successfully provides an ablative procedure for destroying living cells present in a body of a subject. The ablative
20 procedure includes the following steps, which may be executed, for example, using system 10. In a first step of the procedure a plurality of particles are administered to the body of the subject. The particles are similar to the nanoparticles described hereinabove. In a second step, at least one optical pulse is directed toward at least a portion of the cells.

25 According to a preferred embodiment of the present invention the second step may be done by a light transmitting device which may be inserted into the body of the subject. The light transmitting device may be any device known in the art for transmitting, *e.g.*, a laser beam, *e.g.*, a fiber optic bundle. In a third step of the procedure the light transmitting device
30 is used for.

Similarly to the above embodiments, the particles and the pulse (or pulses) are selected and designed so as to provide a local enhancement of an optical field to a power per unit area which is beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

5 According to a preferred embodiment of the present invention the light transmitting device is inserted into the body by either endoscopy or laparoscopy. In addition, the ablation procedure may be executed in parallel to another surgical procedure, while the unwanted cells of the subject are exposed.

10 Suitable metals for forming the metallic nanoparticles or the outer layer of the nanoshells include the noble and coinage metals, but other electrically conductive metals may also be employed. Metals that are particularly well suited for use in shells include but are not limited to gold, silver, copper, platinum, palladium, lead, iron or the like. Gold and silver
15 are preferred. Alloys or non-homogenous mixtures of such metals may also be used.

Gold nanoparticles are suitable markers in biotechnological systems because specific activities of micro-molecules can be retained when coupling micro-molecules to gold nanoparticles. In addition, gold
20 nanoparticles can be easily visualized by electron microscopy. Since gold is inert, gold nano-particles are highly biocompatible.

Suitable dielectric core materials of the nanoshells used in the present invention include, but are not limited to, silicon dioxide, goldsulfide, titanium dioxide, polymethyl methacrylate (PMMA),
25 polystyrene, and macromolecules such as dendrimers. The core of the nanoparticle may also be a combination or a layered combination of dielectric materials such as those listed above.

According to a preferred embodiment of the present invention the living cells may form a part of a tumor. Typical tumors include, but are
30 not limited to, breast tumor, brain tumor, neuroblastoma, thyroid gland

tumor, gestational trophoblastic tumor, uterine sarcoma, carcinoid tumor, colon carcinoma, esophageal carcinoma, hepatocellular carcinoma, liver carcinoma, lymphoma, plasma cell neoplasm, mesothelioma, thymoma, alveolar soft-part sarcoma, angiosarcoma, epithelioid sarcoma, 5 extraskelatal chondrosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocyoma, malignant hemangiopericytoma, malignant mesenchymoma, malignant schwannoma, synovial sarcoma, melanoma, neuroepithelioma, osteosarcoma, leiomyosarcoma, Ewing sarcoma, osteosarcoma, rhabdomyo-sarcoma, 10 hemangiocyoma, myxosarcoma, mesothelioma (*e.g.*, lung mesothelioma), granulosa cell tumor, thecoma cell tumor and Sertoli-Leydig tumor.

Hence, the present invention can be used to treat many types of cancers, such as, but not limited to, vaginal cancer, vulvar cancer, cervical cancer, endometrial cancer, ovarian cancer, rectal cancer, salivary gland 15 cancer, laryngeal cancer, nasopharyngeal cancer, many lung metastases and acute or chronic leukemia (*e.g.*, lymphocytic, Myeloid, hairy cell).

According to a preferred embodiment of the present invention, the affinity component of the nanoparticles includes a moiety which may be, for example an antibody, an antigen, a ligand or a substrate. The 20 techniques of attaching proteins and other chemicals, to the surfaces of metal nanoparticles, are well known in the art. To this end, see, *e.g.*, C. Zhang *et. al.*, *Anal. Chem.* 74, 96 (2002); J. Ni *et. al.* *Anal. Chem.* 71, 4903 (1999); L. Lyon, *et. al.*, *Anal. Chem.* 70, 5177 (1998), the contents of which are hereby incorporated by reference.

25 The following lists some primary antibodies known to specifically bind their associated cytological markers and which are presently employed as affinity components in immunohistochemical stains used for research and, in limited cases, for diagnosis and therapy of various diseases. Anti-estrogen receptor antibody (breast cancer), 30 anti-progesterone receptor antibody (breast cancer), anti-p53 antibody

(multiple cancers), anti-Her-2/neu antibody (multiple cancers), anti-EGFR antibody (epidermal growth factor, multiple cancers), anti-cathepsin D antibody (breast and other cancers), anti-Bcl-2 antibody (apoptotic cells), anti-E-cadherin antibody, anti-CA125 antibody (ovarian and other cancers), anti-CA15-3 antibody (breast cancer), anti-CA19-9 antibody (colon cancer), anti-c-erbB-2 antibody, anti-P-glycoprotein antibody (MDR, multi-drug resistance), anti-CEA antibody (carcinoembryonic antigen), anti-retinoblastoma protein (Rb) antibody, anti-ras oncoprotein (p21) antibody, anti-Lewis X (also called CD15) antibody, anti-Ki-67 antibody (cellular proliferation), anti-PCNA (multiple cancers) antibody, anti-CD3 antibody (T-cells), anti-CD4 antibody (helper T cells), anti-CD5 antibody (T cells), anti-CD7 antibody (thymocytes, immature T cells, NK killer cells), anti-CD8 antibody (suppressor T cells), anti-CD9/p24 antibody (ALL), anti-CD10 (also called CALLA) antibody (common acute lymphoblastic leukemia), anti-CD11c antibody (Monocytes, granulocytes, AML), anti-CD13 antibody (myelomonocytic cells, AML), anti-CD14 antibody (mature monocytes, granulocytes), anti-CD15 antibody (Hodgkin's disease), anti-CD19 antibody (B cells), anti-CD20 antibody (B cells), anti-CD22 antibody (B cells), anti-CD23 antibody (activated B cells, CLL), anti-CD30 antibody (activated T and B cells, Hodgkin's disease), anti-CD31 antibody (angiogenesis marker), anti-CD33 antibody (myeloid cells, AML), anti-CD34 antibody (endothelial stem cells, stromal tumors), anti-CD35 antibody (dendritic cells), anti-CD38 antibody (plasma cells, activated T, B, and myeloid cells), anti-CD41 antibody (platelets, megakaryocytes), anti-LCA/CD45 antibody (leukocyte common antigen), anti-CD45RO antibody (helper, inducer T cells), anti-CD45RA antibody (B cells), anti-CD39, CD100 antibody, anti-CD95/Fas antibody (apoptosis), anti-CD99 antibody (Ewings Sarcoma marker, MIC2 gene product), anti-CD106 antibody (VCAM-1; activated endothelial cells), anti-ubiquitin antibody (Alzheimer's disease), anti-CD71 (transferrin

receptor) antibody, anti-c-myc (oncoprotein and a hapten) antibody, anti-cytokeratins (transferrin receptor) antibody, anti-vimentins (endothelial cells) antibody (B and T cells), anti-HPV proteins (human papillomavirus) antibody, anti-kappa light chains antibody (B cell),
5 anti-lambda light chains antibody (B cell), anti-melanosomes (HMB45) antibody (melanoma), anti-prostate specific antigen (PSA) antibody (prostate cancer), anti-S-100 antibody (melanoma, salivary, glial cells), anti-tau antigen antibody (Alzheimer's disease), anti-fibrin antibody (epithelial cells), anti-keratins antibody, and anti-Tn-antigen antibody
10 (colon carcinoma, adenocarcinomas, and pancreatic cancer).

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various
15 features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with
20 specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this
25 specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that
30 such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A method of destroying living cells, the cells being characterized by an ionization threshold, the method comprising:

providing at least one optical pulse having an optical field power smaller than the ionization threshold of the cells while generating conditions for locally increasing said optical field power per unit area beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

2. The method of claim 1, wherein the cells form a part of an organ.

3. The method of claim 1, wherein the cells form a part of a tumor.

4. The method of claim 1, wherein the cells form a part of a malignant tumor.

5. The method of claim 1, wherein the cells form a part of a blood vessel.

6. The method of claim 1, wherein the cells form a part of a pathological tissue.

7. The method of claim 1, wherein the cells form a part of a restenotic tissue.

8. The method of claim 1, wherein the ionization threshold is from about 10^{10} Watts/cm² to about 10^{14} Watts/cm².

9. The method of claim 1, wherein a duration of said at least one optical pulse is selected so as to avoid heating of the cells by linear absorption.

10. The method of claim 9, wherein said duration is in a femtoseconds time scale.

11. The method of claim 1, wherein a wavelength of said at least one optical pulse is from about 400 nm to about 1300 nm.

12. The method of claim 1, wherein said at least one optical pulse is characterized by a repetition-rate selected from the group consisting of a low repetition-rate and a high repetition rate.

13. The method of claim 12, wherein said repetition-rate is from about 10 pulses/second to about 10^{10} pulses/second.

14. The method of claim 1, wherein said pulses having a high peak-power.

15. The method of claim 1, wherein said pulses having a low average-intensity.

16. The method of claim 14, wherein said peak-power is below the ionization threshold of the living cells.

17. The method of claim 15, wherein said average-intensity is below a heating damage threshold of the living cells.

18. The method of claim 1, wherein said providing at least one optical pulse is by an optical device having peak-power from about 10^5 Watts to about 10^{10} Watts.

19. The method of claim 15, wherein said average-intensity is below 1 Watt/cm².

20. The method of claim 1, further comprising focusing a beam of said at least one optical pulse, so as to increase said optical field power per unit area.

21. The method of claim 20, wherein said focusing is by a converging lens.

22. The method of claim 1, wherein said generating conditions for locally increasing said optical field power per unit area is by a plurality of particles, at least a portion of each of said plurality of particles is made of a conducting material.

23. The method of claim 22, wherein each of said plurality of particles comprises an affinity component having affinity to the living cells.

24. The method of claim 22, wherein a size of each of said plurality of particles is from 1 nm to 200 nm.

25. The method of claim 22, wherein said particles are biocompatible.

26. The method of claim 22, wherein said particles are metallic particles.

27. The method of claim 22, wherein said conducting material is comprised of at least one metal selected from the group consisting of coinage metals, noble metals, transition metals and synthetic metals.

28. The method of claim 27, wherein said synthetic metals are selected from the group consisting of polyacetylene and polyaniline.

29. The method of claim 22, wherein said conducting material is gold.

30. The method of claim 22, wherein said conducting material comprises a metal-like material.

31. The method of claim 22, wherein said conducting material comprises a metal alloy.

32. The method of claim 23, wherein said affinity component comprises a moiety selected from the group consisting of an antibody, an antigen, a ligand and a substrate.

33. The method of claim 32, wherein said moiety is selected so as to ensure attachment of said particles to a predetermined part of the cell, said predetermined part of the cell is selected from the group consisting of nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins, endoplasmic reticulum and Golgi apparatus.

34. The method of claim 22, wherein said particles comprise a conducting shell layer characterized by a shell-thickness having a first radius and a second radius.

35. The method of claim 34, wherein a ratio between said first radius and said second radius is selected so as to obtain a predetermined plasmon-resonance frequency of said particles.

36. The method of claim 35, wherein said predetermined resonance frequency is a near infrared resonance frequency.

37. The method of claim 34, wherein a difference between said first radius and said second radius is from 1 nm to 100 nm.

38. The method of claim 34, wherein said conducting shell layer immediately adjacent to and independently layered upon a non-conducting core layer.

39. The method of claim 38, wherein said non-conducting core layer comprises a dielectric material.

40. The method of claim 39, wherein said dielectric material is selected from the group consisting of silicon dioxide, titanium dioxide, PMMA, polystyrene, and dendrimers.

41. The method of claim 38, wherein said non-conducting core layer comprises a semi-conducting material.

42. The method of claim 38, wherein said non-conducting core layer comprises at least one molecule selected from the group consisting of an organic molecule and an organic super-molecular structure.

43. The method of claim 38, wherein said non-conducting core layer comprises a mixture of non-conducting materials.

44. The method of claim 38, wherein said non-conducting core layer comprises an optically absorbing material.

45. The method of claim 38, wherein said non-conducting core layer comprises a fluorescent material.

46. A method of destroying living cells, the cells being characterized by an ionization threshold, the method comprising:

administrating a plurality of particles to the cells, each of said plurality of particles, at least a portion of each of said plurality of particles is made of a conducting material; and

directing at least one optical pulse toward at least a portion of the cells;

said particles and said at least one optical pulse are selected and designed so as to provide a local enhancement of an optical field to a power per unit area which is beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

47. The method of claim 46, wherein each of said plurality of particles comprises an affinity component having affinity to the living cells.

48. The method of claim 46, wherein the cells form a part of an organ.
49. The method of claim 46, wherein the cells form a part of a tumor.
50. The method of claim 46, wherein the cells form a part of a malignant tumor.
51. The method of claim 46, wherein the cells form a part of a blood vessel.
52. The method of claim 46, wherein the cells form a part of a pathological tissue.
53. The method of claim 46, wherein the cells form a part of a restenotic tissue.
54. The method of claim 46, wherein the ionization threshold is from about 10^{10} Watts/cm² to about 10^{14} Watts/cm².
55. The method of claim 46, wherein a duration of said at least one optical pulse is selected so as to avoid heating of the cells by linear absorption.
56. The method of claim 55, wherein said duration is in a femtoseconds time scale.
57. The method of claim 46, wherein a wavelength of said at least one optical pulse is from about 400 nm to about 1300 nm.

58. The method of claim 46, wherein said at least one optical pulse is characterized by a repetition-rate selected from the group consisting of a low repetition-rate and a high repetition rate.

59. The method of claim 58, wherein said repetition-rate is from about 10 pulses/second to about 10^{10} pulses/second.

60. The method of claim 46, wherein said pulses having a high peak-power.

61. The method of claim 46, wherein said pulses having a low average-intensity.

62. The method of claim 60, wherein a said peak-power is below the ionization threshold of the living cells.

63. The method of claim 61, wherein said average-intensity is below a heating damage threshold of the living cells.

64. The method of claim 46, wherein said directing at least one optical pulse is by an optical device having a peak-power from about 10^5 Watts to about 10^{10} Watts.

65. The method of claim 61, wherein said average-intensity is below 1 Watt/cm².

66. The method of claim 46, further comprising focusing a beam of said at least one optical pulse, so as to increase said optical field power per unit area.

67. The method of claim 66, wherein said focusing is by a converging lens.

68. The method of claim 46, wherein a size of each of said plurality of particles is from 1 nm to 200 nm.

69. The method of claim 46, wherein said particles are biocompatible.

70. The method of claim 46, wherein said particles are metallic particles.

71. The method of claim 46, wherein said conducting material is comprised of at least one metal selected from the group consisting of coinage metals, noble metals, transition metals and synthetic metals.

72. The method of claim 71, wherein said synthetic metals are selected from the group consisting of polyacetylene and polyaniline.

73. The method of claim 46, wherein said conducting material is gold.

74. The method of claim 46, wherein said conducting material comprises a metal-like material.

75. The method of claim 46, wherein said conducting material comprises a metal alloy.

76. The method of claim 47, wherein said affinity component comprises a moiety selected from the group consisting of an antibody, an antigen, a ligand and a substrate.

77. The method of claim 76, wherein said moiety is selected so as to ensure attachment of said particles to a predetermined part of the cell, said predetermined part of the cell is selected from the group consisting of nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins, endoplasmic reticulum and Golgi apparatus.

78. The method of claim 46, wherein said particles comprise a conducting shell layer characterized by a shell-thickness, having a first radius and a second radius.

79. The method of claim 78, wherein a ratio between said first radius and said second radius is selected so as to obtain a predetermined plasmon-resonance frequency of said particles.

80. The method of claim 79, wherein said predetermined resonance frequency is a near infrared resonance frequency.

81. The method of claim 78, wherein a difference between said first radius and said second radius is from 1 nm to 100 nm.

82. The method of claim 78, wherein said conducting shell layer immediately adjacent to and independently layered upon a non-conducting core layer.

83. The method of claim 82, wherein said non-conducting core layer comprises a dielectric material.

84. The method of claim 83, wherein said dielectric material is selected from the group consisting of silicon dioxide, titanium dioxide, PMMA, polystyrene, and dendrimers.

85. The method of claim 82, wherein said non-conducting core layer comprises a semi-conducting material.

86. The method of claim 82, wherein said non-conducting core layer comprises at least one molecule selected from the group consisting of an organic molecule and an organic super-molecular structure.

87. The method of claim 82, wherein said non-conducting core layer comprises a mixture of non-conducting materials.

88. The method of claim 82, wherein said non-conducting core layer comprises an optically absorbing material.

89. The method of claim 82, wherein said non-conducting core layer comprises a fluorescent material.

90. A system for destroying living cells, the cells being characterized by an ionization threshold, the system comprising:

an optical device for providing at least one optical pulse having an optical field power which is smaller than the ionization threshold of the cells; and

a mechanism for locally increasing said optical field power per unit area beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

91. The system of claim 90, wherein said mechanism for locally increasing said optical field power per unit area comprises a plurality of particles, at least a portion of each of said plurality of particles is made of a conducting material.

92. The system of claim 91, wherein each of said plurality of particles comprises an affinity component having affinity to the living cells.

93. The system of claim 91, wherein the cells form a part of an organ.

94. The system of claim 91, wherein the cells form a part of a tumor.

95. The system of claim 91, wherein the cells form a part of a malignant tumor.

96. The system of claim 91, wherein the cells form a part of a blood vessel.

97. The system of claim 91, wherein the cells form a part of a pathological tissue.

98. The system of claim 91, wherein the cells form a part of a restenotic tissue.

99. The system of claim 91, wherein the ionization threshold is from about 10^{10} Watts/cm² to about 10^{14} Watts/cm².

100. The system of claim 91, wherein a duration of said at least one optical pulse is selected so as to avoid heating of the cells by linear absorption.

101. The system of claim 100, wherein said duration is in a femtoseconds time scale.

102. The system of claim 91, wherein a wavelength of said at least one optical pulse is from about 400 nm to about 1300 nm.

103. The system of claim 91, wherein said at least one optical pulse is characterized by a repetition-rate selected from the group consisting of a low repetition-rate and a high repetition rate.

104. The system of claim 103, wherein said repetition-rate is from about 10 pulses/second to about 10^{10} pulses/second.

105. The system of claim 90, wherein said pulses having a high peak-power.

106. The system of claim 90, wherein said pulses having a low average-intensity.

107. The system of claim 105, wherein said peak-power is below the ionization threshold of the living cells.

108. The system of claim 106, wherein said average-intensity is below a heating damage threshold of the living cells.

109. The system of claim 90, wherein said optical device has a peak-power from about 10^5 Watts to about 10^{10} Watts.

110. The method of claim 106, wherein said average-intensity is below 1 Watt/cm².

111. The system of claim 90, further comprising at least one optical element for focusing a beam of said at least one optical pulse, so as to increase said optical field power per unit area.

112. The method of claim 111, wherein said at least one optical element is a converging lens.

113. The system of claim 91, wherein a size of each of said plurality of particles is from 1 nm to 200 nm.

114. The system of claim 91, wherein said particles are biocompatible.

115. The system of claim 91, wherein said particles are metallic particles.

116. The system of claim 91, wherein said conducting material is comprised of at least one metal selected from the group consisting of coinage metals, noble metals, transition metals and synthetic metals.

117. The system of claim 116, wherein said synthetic metals are selected from the group consisting of polyacetylene and polyaniline.

118. The system of claim 91, wherein said conducting material is gold.

119. The system of claim 91, wherein said conducting material comprises a metal-like material.

120. The system of claim 91, wherein said conducting material comprises a metal alloy.

121. The system of claim 92, wherein said affinity component comprises a moiety selected from the group consisting of an antibody, an antigen, a ligand and a substrate.

122. The system of claim 121, wherein said moiety is selected so as to ensure attachment of said particles to a predetermined part of the cell, said predetermined part of the cell is selected from the group consisting of nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins, endoplasmic reticulum and Golgi apparatus.

123. The system of claim 91, wherein said particles comprise a conducting shell layer characterized by a shell-thickness having a first radius and a second radius.

124. The system of claim 123, wherein a ratio between said first radius and said second radius is selected so as to obtain a predetermined plasmon-resonance frequency of said particles.

125. The system of claim 124, wherein said predetermined resonance frequency is a near infrared resonance frequency.

126. The system of claim 123, wherein a difference between said first radius and said second radius is from 1 nm to 100 nm.

127. The system of claim 123, wherein said conducting shell layer immediately adjacent to and independently layered upon a non-conducting core layer.

128. The system of claim 127, wherein said non-conducting core layer comprises a dielectric material.

129. The system of claim 128, wherein said dielectric material is selected from the group consisting of silicon dioxide, titanium dioxide, PMMA, polystyrene, and dendrimers.

130. The system of claim 127, wherein said non-conducting core layer comprises a semi-conducting material.

131. The system of claim 127, wherein said non-conducting core layer comprises at least one molecule selected from the group consisting of an organic molecule and an organic super-molecular structure.

132. The system of claim 127, wherein said non-conducting core layer comprises a mixture of non-conducting materials.

133. The system of claim 127, wherein said non-conducting core layer comprises an optically absorbing material.

134. The system of claim 127, wherein said non-conducting core layer comprises a fluorescent material.

135. An ablative procedure for destroying living cells present in a body of a subject, the cells being characterized by an ionization threshold, the ablative procedure comprising:

administering a plurality of particles to the body of the subject, at least a portion of each of said plurality of particles is made of a conducting material;

directing at least one optical pulse toward at least a portion of the cells;

said particles and said at least one optical pulse are selected and designed so as to provide a local enhancement of an optical field to a power per unit area which is beyond the ionization threshold of the cells, thereby destroying the cells via ionization.

136. The ablative procedure of claim 135, wherein said directing is by inserting a light transmitting device into the body of the subject.

137. The ablative procedure of claim 135, wherein each of said plurality of particles comprises an affinity component having affinity to the living cells.

138. The ablative procedure of claim 136, wherein said inserting said light transmitting device into the body is by endoscopy.

139. The ablative procedure of claim 136, wherein said inserting said light transmitting device into the body is by laparoscopy.

140. The ablative procedure of claim 135, wherein the cells form a part of an organ.

141. The ablative procedure of claim 135, wherein the cells form a part of a tumor.

142. The ablative procedure of claim 135, wherein the cells form a part of a malignant tumor.

143. The ablative procedure of claim 135, wherein the cells form a part of a blood vessel.

144. The ablative procedure of claim 135, wherein the cells form a part of a pathological tissue.

145. The ablative procedure of claim 135, wherein the cells form a part of a restenotic tissue.

146. The ablative procedure of claim 135, wherein the ionization threshold is from about 10^{10} Watts/cm² to about 10^{14} Watts/cm².

147. The ablative procedure of claim 136, wherein said light transmitting device comprise a fiber optic bundle.

148. The ablative procedure of claim 135, wherein a duration of said at least one optical pulse is selected so as to avoid heating of the cells by linear absorption.

149. The ablative procedure of claim 148, wherein said duration is in a femtoseconds time scale.

150. The ablative procedure of claim 135, wherein a wavelength of said at least one optical pulse is from about 400 nm to about 1300 nm.

151. The ablative procedure of claim 135, wherein said at least one optical pulse is characterized by a repetition-rate selected from the group consisting of a low repetition-rate and a high repetition rate.

152. The ablative procedure of claim 151, wherein said repetition-rate is from about 10 pulses/second to about 10^{10} pulses/second.

153. The ablative procedure of claim 135, wherein said pulses having a high peak-power.

154. The ablative procedure of claim 135, wherein said pulses having a low average-intensity.

155. The ablative procedure of claim 153, wherein said peak-power is below the ionization threshold of the living cells.

156. The ablative procedure of claim 154, wherein said average-intensity is below a heating damage threshold of the living cells.

157. The ablative procedure of claim 154, wherein said average-intensity is below Watt/cm^2 .

158. The ablative procedure of claim 136, wherein said light transmitting device comprises at least one optical element for focusing a beam of said at least one optical pulse, so as to increase said optical field power per unit area.

159. The ablative procedure of claim 158, wherein said at least one optical element is a converging lens.

160. The ablative procedure of claim 135, wherein a size of each of said plurality of particles is from 1 nm to 200 nm.

161. The ablative procedure of claim 135, wherein said particles are biocompatible.

162. The ablative procedure of claim 135, wherein said particles are metallic particles.

163. The ablative procedure of claim 135, wherein said conducting material is comprised of at least one metal selected from the group consisting of coinage metals, noble metals, transition metals and synthetic metals.

164. The ablative procedure of claim 163, wherein said synthetic metals are selected from the group consisting of polyacetylene and polyaniline.

165. The ablative procedure of claim 135, wherein said conducting material is gold.

166. The ablative procedure of claim 135, wherein said conducting material comprises a metal-like material.

167. The ablative procedure of claim 135, wherein said conducting material comprises a metal alloy.

168. The ablative procedure of claim 137, wherein said affinity component comprises a moiety selected from the group consisting of an antibody, an antigen, a ligand and a substrate.

169. The ablative procedure of claim 168, wherein said moiety is selected so as to ensure attachment of said particles to a predetermined part of the cell, said predetermined part of the cell is selected from the group consisting of nucleus, nucleolus, mitochondria, membrane, DNA, RNA, proteins, endoplasmic reticulum and Golgi apparatus.

170. The ablative procedure of claim 135, wherein said particles comprise a conducting shell layer characterized by a shell-thickness, having a first radius and a second radius.

171. The ablative procedure of claim 170, wherein a ratio between said first radius and said second radius is selected so as to obtain a predetermined plasmon-resonance frequency of said particles.

172. The ablative procedure of claim 171, wherein said predetermined resonance frequency is a near infrared resonance frequency.

173. The ablative procedure of claim 170, wherein a difference between said first radius and said second radius is from 1 nm to 100 nm.

174. The ablative procedure of claim 170, wherein said conducting shell layer immediately adjacent to and independently layered upon a non-conducting core layer.

175. The ablative procedure of claim 174, wherein said non-conducting core layer comprises a dielectric material.

176. The ablative procedure of claim 175, wherein said dielectric material is selected from the group consisting of silicon dioxide, titanium dioxide, PMMA, polystyrene, and dendrimers.

177. The ablative procedure of claim 174, wherein said non-conducting core layer comprises a semi-conducting material.

178. The ablative procedure of claim 174, wherein said non-conducting core layer comprises at least one molecule selected from the group consisting of an organic molecule and an organic super-molecular structure.

179. The ablative procedure of claim 174, wherein said non-conducting core layer comprises a mixture of non-conducting materials.

180. The ablative procedure of claim 174, wherein said non-conducting core layer comprises an optically absorbing material.

181. The ablative procedure of claim 174, wherein said non-conducting core layer comprises a fluorescent material.

182. A light transmitting device for destroying living cells present in a body of a subject, the device comprising:

an optical device for emitting at least one optical pulse having a duration in a femtosecond time scale; and

a waveguide for guiding said optical pulses into a body of a subject; said waveguide having an emission face, through which said optical pulses are emitted to the living cells, thereby destructing the cells via ionization.

183. The light transmitting device of claim 182, wherein said optical pulses having a wavelength from about 400 nm to about 1300 nm.

184. The light transmitting device of claim 182, wherein said waveguide comprise a fiber optic bundle.

185. The light transmitting device of claim 182, wherein said waveguide is sterile.

186. The light transmitting device of claim 182, wherein said waveguide is covered by a disposable sterile coat.

187. The light transmitting device of claim 182, wherein said at least one optical pulse is characterized by a repetition-rate selected from the group consisting of a low repetition-rate and a high repetition rate.

188. The light transmitting device of claim 187, wherein said repetition-rate is from about 10 pulses/second to about 10^{10} pulses/second.

189. The light transmitting device of claim 182, wherein said pulses having a high peak-power.

190. The light transmitting device of claim 182, wherein said pulses having a low average-intensity.

191. The light transmitting device of claim 182, wherein said optical device has a peak-power from about 10^5 Watts to about 10^{10} Watts.

192. The light transmitting device of claim 190, wherein said average-intensity is below 1 Watts/cm².

Dr. Gal Ehrlich
Patent Attorney
G. E. Ehrlich (1995) Ltd.
28 Bezalel Street
52521 Ramat-Gan

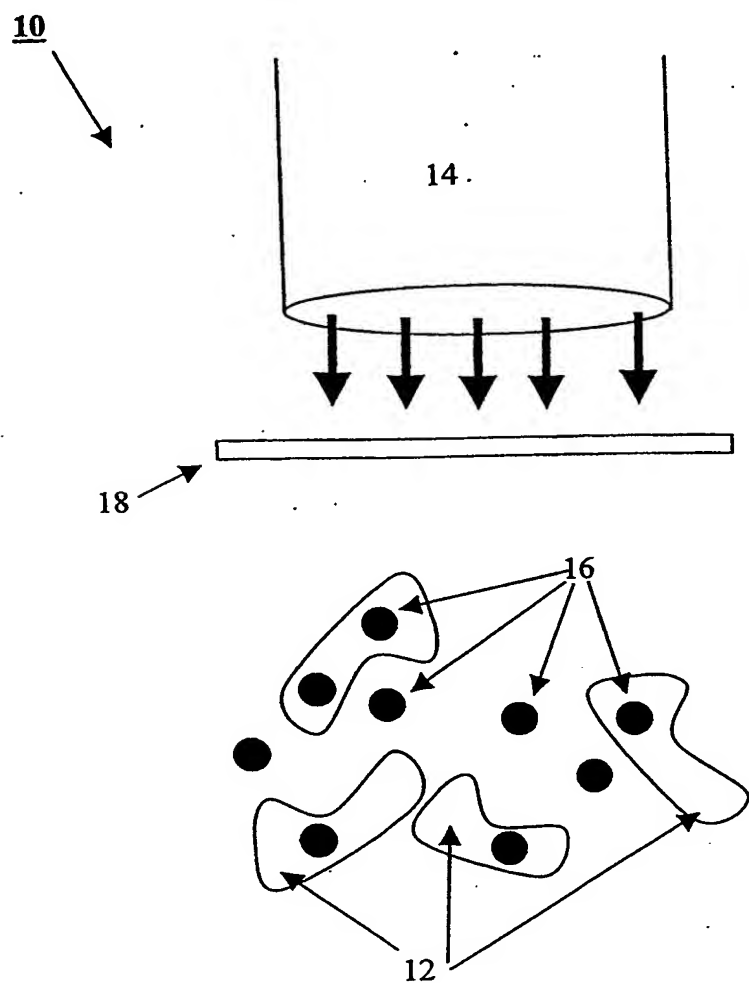


Fig. 1

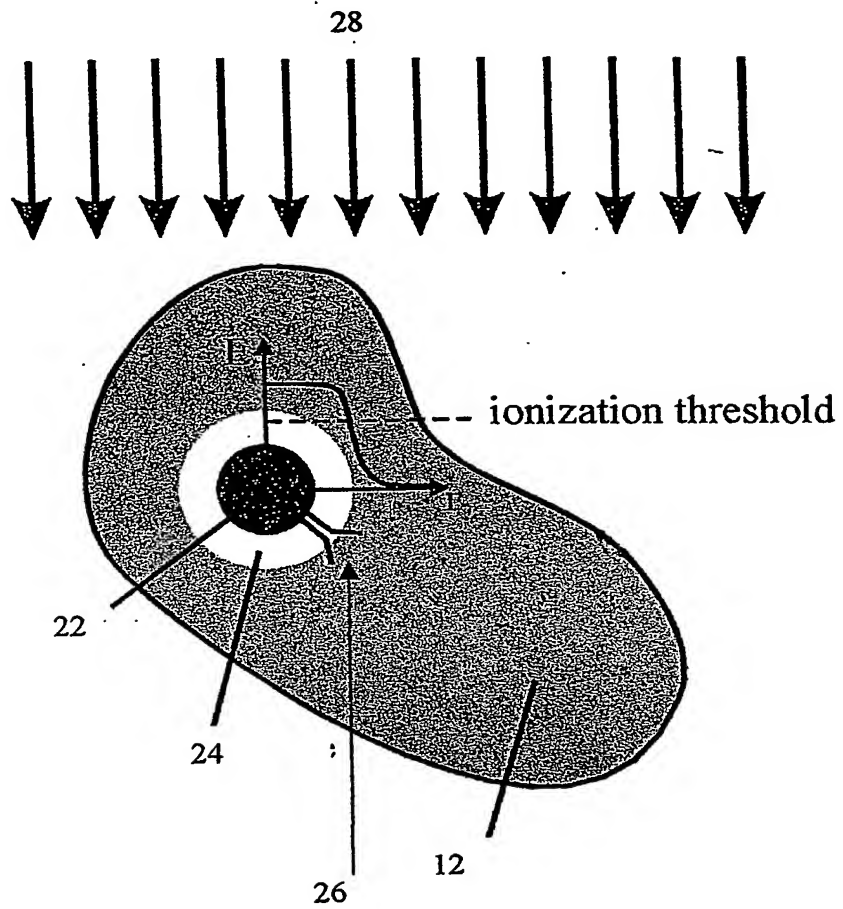


Fig. 2

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.